

Aus der Chirurgischen Universitätsklinik Basel

Vorsteher: Prof. Dr. med. R. Nissen

Arbeit unter Leitung von PD. Dr. M. Allgöwer

A comparative study of various enzymatic debriding agents

Inaugural-Dissertation

zur Erlangung der Doktorwürde der Medizinischen

Fakultät der Universität Basel

vorgelegt von

Erich H. Schultz

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The concept of hastening the healing time of wounds by removing necrotic tissue with proteolytic enzymes is not new. Thiersch and Nussbaum⁴⁹ already described the use of pepsin in the treatment of necrotic tumors in 1870 but recorded no success. Schiff⁴⁰ proved the possibility of enzyme treatment early in 1900 by showing that trypsin digested protein substances without eroding the blood vessels. Saphra³⁹, Niedermeyer³⁴ und Katz²⁶ studied the effects of trypsin on infected and necrotic wounds. In 1943 Cooper, Hodge and Beard¹⁰ reported on a method of enzymatic digestion for the removal of dead tissue. Enzymatic debridement was first introduced into burn therapy by Greuer¹⁹ in 1945. Further reports were soon to follow by Stucke⁴⁵ in 1949, Reiser³⁶ in 1950 and Altemeier² in 1951.

In third degree burns of limited extent the necrotic material can be removed by surgical excision³⁷. However, it should be kept in mind that early determination of the extent of tissue demarcation in a severe burn is extremely difficult. This was clearly shown by the studies of Jackson²⁴ as well as those of Moritz and Henriques³².

To overcome this problem of debridement, plant^{2, 3, 10, 18, 53}, animal^{3, 10, 13, 32}, bacterial^{2, 7, 43, 50} enzymes as well as organic^{8, 9, 27, 29, 30} and inorganic^{42, 47} acids have been tried. All authors have claimed a certain degree of success. It is, therefore, the purpose of this investigation to compare various enzymatic preparations and to give a critical evaluation of them in regards to their usefulness in removing necrotic material resulting from third degree burns.

Materials & Methods

Rabbits ranging in weight from 3 to 3.5 kg were used, their trunks shorn and the dorsolateral areas to be burned shaved. Anaesthesia was induced by intravenous Nembutal using 0.6 cc per kg.

A modification of the ear chamber developed by Allgöwer¹ which completely isolated the burn, protecting from licking, scratching and infection was used. Figure 1 illustrates the details of the wound-chamber (above) and presents below a cross-section of the chamber as mounted on the animal's

The material for this investigation was supplied by Röhm & Haas G.m.b.H., Darmstadt, Germany.

back. This method permitted observation as well as dressing of the wound without undue irritation to surrounding tissue or the entire animal and served as an assurance that the test substance was always in place. The wound-chamber was mounted under sterile conditions, four to each animal, i. e. two to each side. It should be noted that during the entire course of the

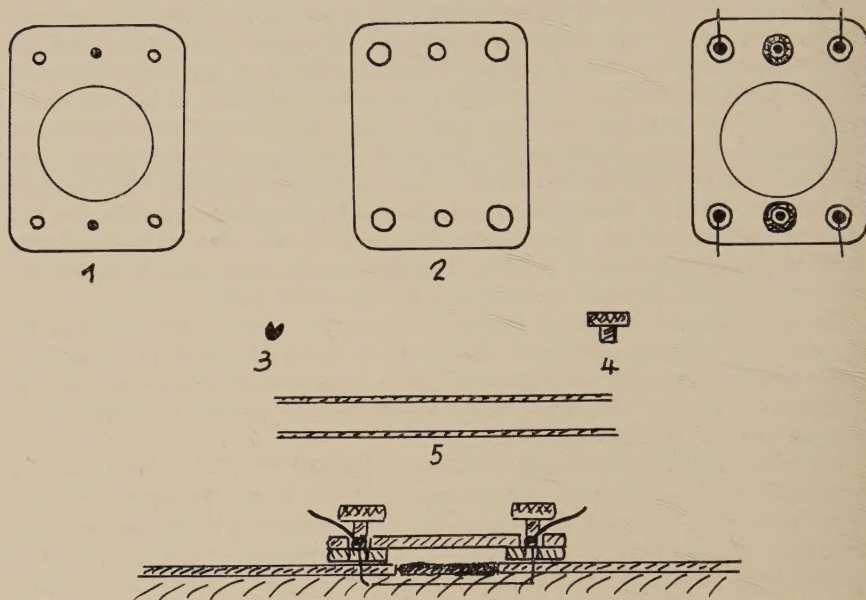


Fig. 1. Showing the wound chamber employed in this experiment. Above: Detail of various parts: 1 Base plate, 2 Chamber cover, 3 Lead slug, 4 Nut, 5 Surgical wire. Below: Cross-section of the mounted wound chamber.

experiment burns were applied to the same body region. A no. 4 hypodermic needle was forced through the skin of the animal and allowed to emerge at a distance which corresponded to the interval between the holes of the base plate. Two such needles were applied parallel to each other and surgical wire threaded through each. The needles were then removed so that the base plate could now be attached to the two wires protruding through the skin. Each end of the wire was passed through a corresponding hole in the base plate and the latter secured by attaching four lead slugs to the individual wires. Once the chamber was mounted the standard burn was applied.

Standard burns were applied by using a specially constructed copper iron with a built-in thermostat which permitted a constant temperature throughout the entire period of application. At a temperature of 150 degrees C. for

8 sec. and a pressure of 745 gms. a full thickness skin burn of 2 cm diameter was obtained. All burns were immediately dressed and the wet pressure dressings were held in place by the cover of the wound chamber.

The animals were fed a balanced diet and housed in wire cages at a room temperature of 23° C. The wounds were dressed once daily, always at the same time of day. The enzyme solutions used were always freshly prepared at the time of dressing. Wounds were photographed on the first and seventh day post-burn. Planimetric measurements of wound area were made by tracing daily the outline of these wounds unto cellophane. This procedure gave a measure of the rate of wound healing.

Each animal acted as its own control, and all burns were covered with wet pressure dressings. All control burns were treated daily with Ringer's. The various enzymes used are listed in table I, together with the concentrations applied. Once a wound was found to be debrided and clean it was handled by the open-air method. The burned site was considered debrided and clean once the eschar had become digested and the wound base presented a bright red, healthy granulation. A wound was considered healed when the entire base was covered by epithelium.

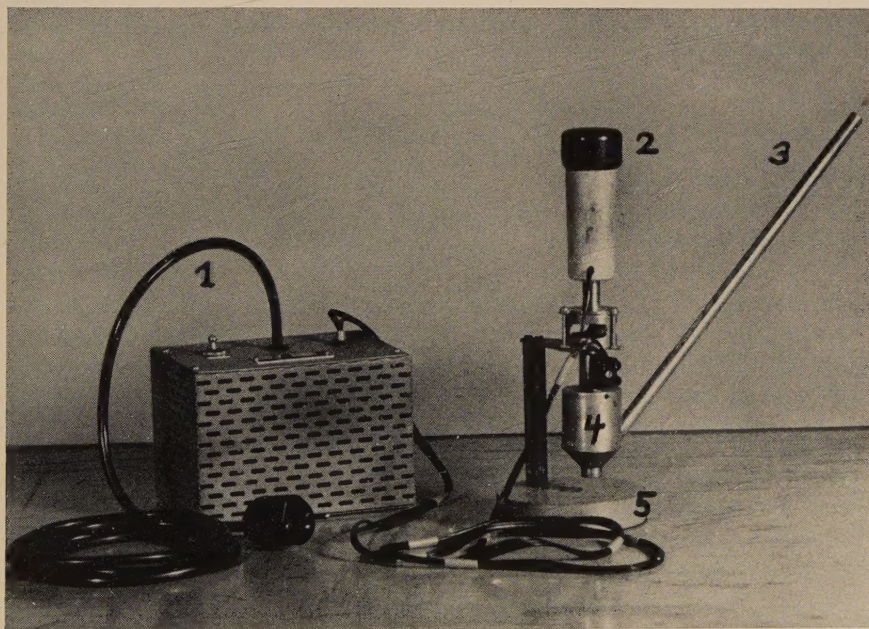


Fig. 2. Apparatus used to set standardized burn. 1 Thermostat, 2 Temperature regulator, 3 Thermometer, 4 Copper iron, 5 Stand.

TABLE I

Product and manufacturer	Content according to the manufacturer's description*	Concentration used
Pyruvic acid	Pyruvic acid ph 1.9	Added to an 8% corn-starch paste
Tryptodigest Sanabo Wien, Austria	Purified lyophilized trypsin plus 5% Anesthesin	According to the manufacturer's directions with the exception that the prep. were applied only once a day.
Trypure Novo Novo Therapeutisk Lab. A/S, Copenhagen N, Denmark	Purified dialized and lyophilized crystalline trypsin plus Sorensen's Phosphate buffer	According to the manufacturer's directions with the exception that the prep. were applied only once a day.
Leukocillase Dauelsberg & Co. Göttingen, Germany	15 Units Trypsin 50,000 I.E. Penicillin G—Na 25,000 Units Streptomycin sulfate 25,000 Units Dihydrostreptomycin sulfate	According to the manufacturer's directions with the exception that the prep. were applied only once a day.
Nekrosolva Kali-Chemie AG Hannover, Germany	Pancreas ferment plus glycerin, bicarbonate and Nipagin	According to the manufacturer's directions with the exception that the prep. were applied only once a day.
Pyosolva Kali-Chemie AG Hannover, Germany	Trypsin plus activator	According to the manufacturer's directions with the exception that the prep. were applied only once a day.

* Critical comparison is hampered by the lack of standardization among the preparations.

PZ 44 Röhm & Haas G.m.b.H. Darmstadt, Germany	8,000 Protease Units of Papain	According to the manufacturer's directions with the exception that the prep. were applied only once a day.
Jatrosin Röhm & Haas G.m.b.H. Darmstadt, Germany	15,000 Protease Units of pancreas ferment	8% solution in Ringer's
Tryptar Armour Lab. U.S.A.	Purified crystalline trypsin of mammalian pancreas plus a Sorensen's Phosphate buffer	As directed with the exception that the prep. were applied only once a day.
Varidase Lederle, N. Y. Amer. Cyanamid Co. U.S.A.	100,000 Christensen Units Streptokinase and at least 25,000 Units Streptodornase	As directed with the exception that the prep. were applied only once a day.
Biotrase Hamol AG Zürich Switzerland	Purified trypsin 10% Ca-N-Oxymethyl- glutamate 10% Sulfanilamid Carbamid and Excipients	As directed with the exception that the prep. were applied only once a day.

Similar tests were carried out in young pigs whose skin closely approximates anatomically that of man. Two types of burns were performed in these animals. In one series a small burn was made resembling that described for the rabbit by using a temperature of 150° C for 15 sec. and a pressure of 745 gms. This resulted in a full thickness, third degree burn. In another series, large area burns were made by applying an electric hotplate to the back of the pig at a temperature of 175° C for 15 sec. This resulted in a third degree burn that did not reach the muscle layer. By prolonging the exposure time to 30 sec. a burn reaching the muscle layer was obtained.

The pigs ranged in weight from 18 to 22 kg.

The data represents 500 experimental burns performed on 125 rabbits and 30 burns performed on 4 pigs.

Results

In the control wounds the eschar loosened and broke off at the periphery slowly working in toward the center, keeping a soft necrotic base almost to the end. Average healing time in 50 control wounds was 30 days.

Pyruvic acid succeeded in softening and removing the necrotic material in one piece, the separation beginning at the periphery and proceeding centralwards, requiring an average of 19.7 days. During treatment a slight irritation of the adjacent tissue was observed and a bright red granulation was not obtained. Average healing time was 26.8 days.

Varidase was not very successful in removing the eschar and was active only at the periphery of the wound making here a bloody granulating ring which worked its way very slowly toward the center requiring 20.1 days, for cleaning. There was no irritation and the wound was completely covered by epithelium in 31.6 days.

Trypure Novo easily removed the upper necrotic layer cleaning the base in 12 days. There was no irritation and the wound healed in 26.6 days.

Leukocillase dissolved the sludge and cleaned the wound in 16.1 days. It did not irritate the adjacent tissue and the wounds healed in 25.2 days.

Biotrase caused no irritation, required 16.1 days for cleaning. The wounds were healed after 29.8 days.

Pyosolva caused strong irritation of the surrounding tissue, cleaning the wounds in 9.7 days. Healing took 23.7 days.

PZ 44 damaged the adjacent tissue, cleaned in 12 days. The wounds healed in 23.3 days.

Nekrosolva did not irritate and cleaned the wound in 16.1 days. Healing required 21.0 days.

Tryptar showed no irritation, cleaned the wounds in 11.9 days and healing was complete in 25.2 days.

Jatrosin gave the best results. Softening of the necrotic tissue was complete in 2 to 3 days. On the 6th day, the sludge, a thick sticky milky layer could be carried off leaving a clean red base. There was no irritation and wound healing was complete in an average time of 20 days.

Table IIa and IIb present a general summary of the experiments performed on rabbits and the data obtained. Although the number of wounds observed for healing time when using enzymes is small in comparison to the controls the majority do show a definite reduction in healing time. Table III represents the data obtained on burned pigs. The number of wounds is too small for critical evaluation, but nevertheless the difference in cleaning rate seems obvious.

Figures 3 to 6 show typical experiments with small standardized burns as well as with extensive burns in pigs.

TABLE IIa

Comparison of the cleaning time of the various products with standardized third degree burns on rabbits using a temperature of 150° C for 8 sec. with a pressure of 745 gms.

Product	number	average cleaning time in days
Controls	50	eschar stays until wound healing completed
Pyruvic acid	25	20
Tryptodigest	25	14
Trypure Novo	25	12
Leukocillase	25	16
Nekrosolva	25	16
Pyosolva	25	10
PZ 44	25	12
Jatrosin	40	6
Tryptar	25	12
Varidase	25	20
Biotrase	25	16

TABLE IIb

Comparison of the effectiveness of the various preparations on healing time of a standardized third degree burn on rabbits using a temperature of 150° C for 8 sec. with a pressure of 745 gms.

Products	Number	average healing time in days
Ringer's control	50	30
Pyruvic acid	6	27
Tryptodigest	6	27
Trypure Novo	6	27
Leukocillase	6	25
Nekrosolva	6	24
Pyosolva	6	24
PZ 44	6	23
Jatrosin	40	20
Tryptar	6	25
Varidase	6	32
Biotrase	6	30

TABLE III

Comparison of the effectiveness of various substances on cleaning in standard third degree burns in pigs using a temperature of 150° C for 15 sec. with a pressure of 745 gms.

Small burns			Large burns	
Product	n	cleaning time in days	Temperature and time	cleaning time of large area burn
Jatrosin	10	6	175° C for 15 sec. 30 sec.	7
				11
Biotrase	2	15		
Leukocillase	2	15		
Tryptodigest	2	13		
Trypure Novo	2	11		
Pyosolva	2	10		
Empykratin N*	2	15		
Nekrosolva	2	15		
Varidase	2	18		

* Empykratin N, Schering, Berlin, Germany, Pancreas ferment plus Cellulose, Glycocol and Na bicarbonate.

Discussion

Application of a good debriding agent should result in early removal of the eschar, thus preventing infection, permitting early grafting, reducing further plasma loss and minimising contraction and scarring. The debriding agent must not be damaging to living tissue, should allow granulation formation to proceed normally and be non-toxic either locally or systemically.

A number of investigators have claimed successful wound debridement by using acids and enzymes. Clinically, the results have not been universally in agreement. Most studies lack standardization, both with regard to procedure of burning and size of wound. It has thus become very difficult to evaluate the different results. The difficulty of differentiating a deep second degree from a third degree burn also adds to the unreliability of many clinical reports. Temperature, length of exposure to the burning agent and the latent period between burning and the start of treatment are all factors which must be considered when evaluating chemical wound debridement.

In the work presented an endeavor was made to avoid as many unknown factors as possible. Starting with healthy animals on a balanced diet and kept at a constant room temperature a standardized third degree burn was made which healed on the average in 30 days. After a pilot study with control burns, the cleaning and healing time were then determined by comparing the preparations listed. All substances tested resulted in a decrease in cleaning time and, with the exception of Varidase, in a definite reduction in the time of healing.

Of the substances tested, Jatrosin appeared to possess the following advantages: 1. minimal cleaning time (6.1 days). The reduction in cleaning time when compared to other substances was statistically significant ($p < 0.001$) when evaluated by means of the t-test.

2. Probably as a result of the reduction in cleaning time, complete healing occurred earlier, although there is no definite time interval between cleaning and complete healing of the wound.

3. In contrast to the other substances wounds treated with 2741 evidenced no irritation. In a small series in which the wounds were dressed three times daily irritation, such as increased exsudation, occasional bleeding, and increase in the wound area was noted with all substances. This irritation was frequently not only conferred to the burn but extended to surrounding apparently healthy tissue.

Similar burns as in the rabbit were made in the pig, an animal whose skin structure more closely resembles that of man. It is interesting that an increase in time of exposure was required in order to produce a burn similar in depth to the one produced in the rabbit. The number of experiments performed are too few to allow for definite conclusions. However, a general trend in the reduction of cleaning time was noted that closely resembled the findings in the rabbit. The large area burns demonstrated that cleaning time is prolonged when the depth of a burn is increased.

Conclusions

1. A new enzymatic debriding agent was evaluated experimentally in the rabbit and pig, and its effectiveness compared to other debriding agents.
2. The agent investigated produced a significant lowering of cleaning and healing time when tested in a standard burn.



Fig. 3

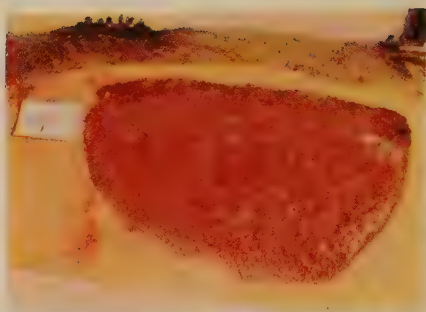


Fig. 5

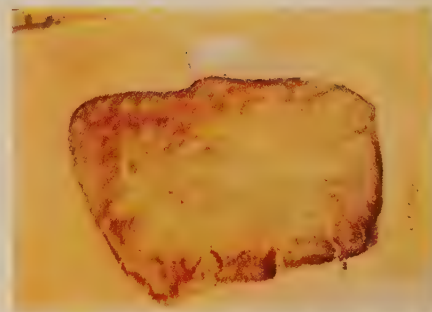


Fig. 6

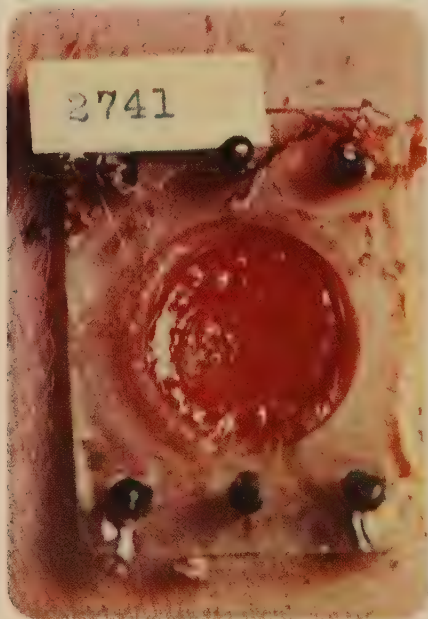


Fig. 4

Fig. 3. Small, standardized burn in pig. A freshly set full thickness skin burn using a temperature of 150°C . for 15 sec. using a pressure of 745 gms.

Fig. 4. Same burn as in Figure 3 after treatment with Jatrosin on the 7th day. Eschar is completely removed and good granulation is present.

Fig. 5 and 6. Third degree burns in pig using temperature of 175°C for 15 sec.

Fig. 5. After treatment with Jatrosin for 7 days.

Fig. 6. After treatment with Ringer's for 7 days.

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Curriculum Vitae

Ich, Erich H. Schultz, Bürger der Vereinigten Staaten von Amerika, wurde am 3. November 1924 in Iserlohn, Deutschland, geboren.

1927 übersiedelte ich nach Amerika. Im Jahre 1943 bestand ich an dem Gymnasium (Islip High School) die Matura. Im Frühling 1943 trat ich in den Militärdienst ein.

Aus dem Militärdienst zurückgekehrt (1946), setzte ich meine Studien am Washington Sq. College, New York Universität, fort und schloß sie im Jahre 1949 mit dem „Bachelor of Arts“ Diplom ab.

Von 1949 bis 1950 erweiterte ich meine Studien in Chemie an der New York Universität und begab mich anschließend in die Schweiz, um an der Universität Bern Medizin zu studieren. Im Herbst 1953 bestand ich das zweite propädeutische Examen an der Universität Erlangen, Deutschland, setzte anschließend meine Studien an der Universität Basel fort und bestand meine „Fachprüfung für Ärzte“ am 17. Mai 1957.

